

REACHING THE THERAPEUTIC GOAL IN HYPERTENSION: RESULTS FROM THE CANADIAN VALSARTAN OBSERVATIONAL STUDY (DIOVANTAGE 4)

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ABSTRACT

Background

Hypertension is a leading cause of death worldwide, and a major public health problem in Canada. Despite treatment guidelines and availability of therapies for blood pressure (BP) management, treatment of hypertension remains sub-optimal.

Objectives

The objectives of this trial are to observe BP reduction, compliance and regimen changes 3 months after initiation of valsartan alone or with hydrochlorothiazide and optimized patient support.

Methods

As of February 2007, 34,033 patients with essential hypertension and prescribed valsartan alone or with hydrochlorothiazide for BP management were enrolled across 2,125 Canadian sites. Patients were newly diagnosed (38%), switched from another anti-hypertensive agent (38%) or received valsartan with or without hydrochlorothiazide as added therapy (20%). All patients were offered a home blood pressure monitor, access to nursing support and educational materials. Patients were assessed after 3 months for compliance, therapeutic response, and need for treatment modifications.

Results

In this interim analysis, after 3 months of treatment, 95% of patients reported being compliant with therapy and 59% achieved target BP (<140/90 mmHg). In the evaluable population (n=15,200), significant reductions in mean systolic (-18.5±19.3 mmHg, p<0.0001) and diastolic (-9.4±11.2 mmHg; p<0.0001) BP were observed. For patients not reaching target BP goals, no change in treatment was instituted in 55% of cases.

Conclusions

This observational study demonstrates the benefits of valsartan alone or with hydrochlorothiazide and optimized patient support in BP management of patients with essential hypertension. Interestingly, no modification to the anti-hypertensive regimen was done in 55% of patients not having reached treatment goals.

Key Words: *Blood pressure, compliance, hypertension, valsartan, health care delivery, behavior modification*

Hypertension is a major public health problem in Canada and in the international community. The World Health Organization has

estimated that high blood pressure causes one in every eight deaths, making hypertension the third leading cause of death in the world.¹ If left

uncontrolled, hypertension can lead to kidney failure, myocardial infarction, congestive heart failure, stroke and other cardiovascular complications.² Hypertension also frequently complicates the evolution of diabetes and chronic obstructive pulmonary disease. Numerous studies have clearly demonstrated that lowering blood pressure in patients with hypertension reduces the risk of major cardiac events.³⁻⁵ Despite availability of safe and effective treatments, hypertension management remains sub-optimal.⁶⁻⁸

The Canadian Hypertension Education Program⁹ was initiated in 1999 as part of a national strategic plan to improve hypertension management and generates annual evidence-based hypertension management recommendations. The Canadian Recommendations for the Management of Hypertension¹⁰⁻¹² endorse the greater use of non-office-based measures of blood pressure control, greater emphasis on the identification of other cardiovascular risk factors, and the need for individualized therapy. Additionally, the recommendations stress that efforts to improve compliance to antihypertensive treatment should include a multifaceted proactive approach, such as encouraging patients to take greater responsibility in monitoring their own blood pressure, adjusting lifestyle choices, and providing education to patients and their families. Target blood pressures of less than 140/90 mmHg in all patients, and less than 130/80 mmHg in those with diabetes mellitus or chronic kidney disease, are recommended. Both the Canadian Hypertension Education Program and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure¹³ stress the importance of assessing global cardiovascular risk in patients with hypertension and the importance of improving patient compliance. As a result of the Canadian Hypertension Education Program, hypertension management has improved in Canada in the past decade.¹⁰ Yet, there exists an opportunity for improved patient management through increased patient and healthcare provider awareness, prescription of effective anti-hypertensive treatments, intensified patient education, and structured patient support.¹⁴

Valsartan is part of the class of angiotensin II receptor blockers (ARBs). Published data demonstrate that valsartan has a favorable safety and efficacy profile and represents a good option

for a wide range of hypertensive patients.¹⁵⁻¹⁷ Valsartan is approved in Canada for the treatment of mild to moderate essential hypertension and to reduce cardiovascular mortality in high risk, post myocardial infarction patients. The Diovantage 4 study is an ongoing 'real-world' observational trial designed to collect data in a natural setting in patients who have access to education and nursing support, as well as home blood pressure monitoring to encourage compliance. The primary objective of the Diovantage 4 trial was to observe the systolic and diastolic blood pressure reductions in patients with essential hypertension receiving valsartan with or without hydrochlorothiazide after three months of treatment in a naturalistic setting. The study also sought to assess, after 3 months of therapy, the number of patients who have reached the target blood pressure as recommended in the Canadian guidelines. Additionally, the effects of patient status, severity of pre-treatment hypertension, prescribed dose/regimen, compliance, age, gender, and race on treatment response was explored. The conduct of an interim analysis, to provide feedback to participating investigators, was pre-specified in the protocol. This article presents the results of the interim analysis on data collected up to February 2007.

METHODS

Patient Population

The inclusion criteria consisted of patients at least 18 years of age, with a diagnosis of essential hypertension who required pharmacologic treatment, and for whom the physician had independently decided to prescribe valsartan alone (Diovan) or valsartan with hydrochlorothiazide (Diovan HCT) for the first time or to restart a patient after a prolonged lapse in treatment (more than 12 months). Patients were excluded if they were allergic to valsartan and/or hydrochlorothiazide or if they had any conditions which were known contraindications to these medications. Pregnant or lactating women were excluded, as were patients involved in any other compliance study at the time of enrollment into Diovantage 4. The study was conducted in accordance with the Guidelines for Good Clinical Practice and the Declaration of Helsinki of the World Medical Association, and was approved by an independent Institutional Review Board. All participants

included in this analysis provided written informed consent.

Study Design and Procedures

Enrolled patients were provided with a home blood pressure monitor, educational materials, and access to a nurse support telephone line. Additional educational materials were mailed to the patient's home 1 and 3 months after enrollment. As part of standard practice, after approximately 3 months of therapy, patients visited their physicians to monitor progress. At this visit, physicians documented the patients' blood pressure readings and made treatment adjustments as needed.

To evaluate compliance during the study, patients were instructed to complete diaries and were asked to self-report their level of compliance to their physician at the month 3 visit. Compliance was defined as patients having taken valsartan alone or with hydrochlorothiazide everyday, almost everyday or on average, every other day. All other responses were considered non-compliant. Physicians were expected to perform any necessary patient medical monitoring, including blood pressure monitoring and laboratory tests as part of standard practice. The diagnosis of hypertension was made either based on investigator's review of patient's past medical history or based on routine office blood pressure measurements.

Statistical Analysis

Demographic characteristics were summarized for all patients enrolled in the trial. The evaluable population was defined as all patients with both systolic and diastolic blood pressure measurements recorded at baseline and at the 3 month follow-up

visit, and with greater than 21 days between both visits. The primary efficacy parameter was the change in systolic and diastolic blood pressure from baseline to 3 months in evaluable patients. An interim database lock occurred at the end of February 2007. Statistical testing at the 5% significance level was carried out for change over time within one group using a paired-t-test while t-tests for independent samples were used to test between two groups. Additionally, the response rate and the proportion of patients having reached target blood pressure level, according to Canadian guidelines (less than 140/90 mmHg in all patients, and less than 130/80 mmHg in those with diabetes mellitus), after 3 months of therapy were evaluated. Patient response to treatment was also evaluated by patient status, study medication dose, baseline blood pressure, gender, age, and race using descriptive statistics. All data analyses were carried out using SAS® software (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

Between October 2003 and February 2007, 34,033 of the planned total enrolled population of approximately 40,000 patients with essential hypertension were recruited into the Diovanage 4 observational study from 2,125 study sites across Canada. For all patients enrolled, the overall mean (\pm SD) patient age was 59.5 \pm 13.1 years, with a mean baseline systolic blood pressure of 154.1 \pm 17.4 mmHg and a mean baseline diastolic blood pressure of 90.0 \pm 10.8 mmHg; 50.2% were women; 80% were Caucasians; 35% were \geq 65 years of age; 20% had diabetes; and 33% had dyslipidemia (Table 1).

TABLE 1 Demographic Characteristics of all Enrolled Patients (n=34,033)

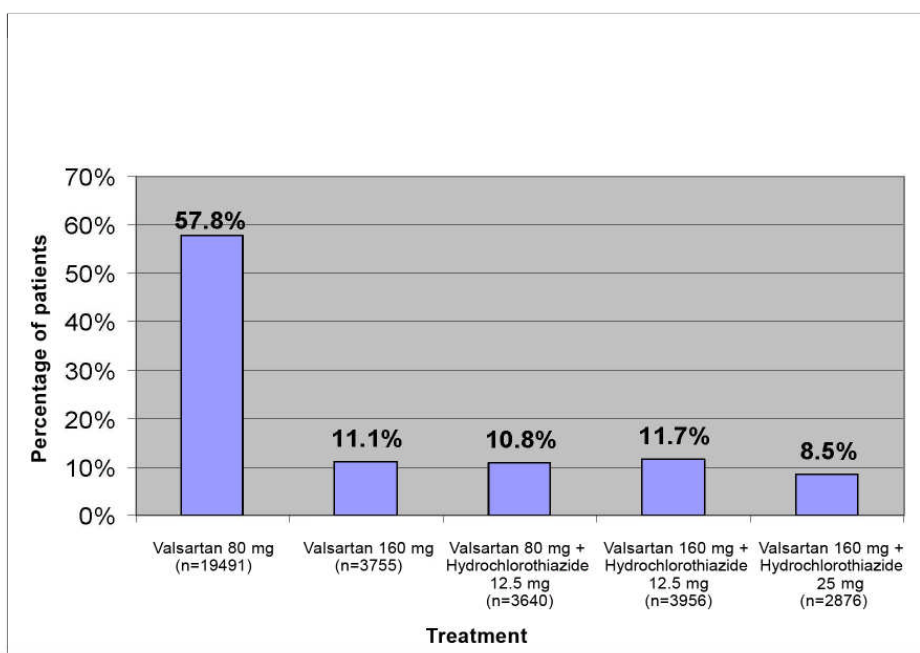
Characteristic	Value
Mean age (years)	59.5 \pm 13.1
% Elderly patients (\geq 65 years)	35%
Gender (%)	49.8% Male, 50.2% Female
Patients with diabetes (%)	20%
Patients with dyslipidemia (%)	33%
Mean systolic blood pressure (mmHg)	154.1 \pm 17.4
Mean diastolic blood pressure (mmHg)	90.0 \pm 10.8
Race (%)	79.5%Caucasion, 11.0% Asian, 3.6% Black, 6.0% Other

The majority of patients were either newly diagnosed (38%) or switched to valsartan alone or with hydrochlorothiazide (38%), while 20% of patients received valsartan as added therapy. Of the available valsartan prescribing options (80 mg valsartan, 160 mg valsartan, 80 mg valsartan/12.5 mg hydrochlorothiazide, 160 mg valsartan/12.5 mg hydrochlorothiazide, or 160 mg valsartan/25 mg hydrochlorothiazide) the majority of patients (57.8%) were placed on 80 mg of valsartan alone (Figure 1).

The largest patient group (n=9,080) was newly diagnosed patients who were prescribed valsartan 80 mg. With respect to switching from other medications, the most commonly switched medication was angiotensin converting enzyme (ACE) inhibitors (41%), with other ARB agents being the second most common (24%). Patients were seen by a physician for a follow-up visit an average of 115 days after study initiation, with a median of 99 days.

FIG. 1 Treatment Prescribed at Baseline for Enrolled Patients (n=33,718)

Figure 1.



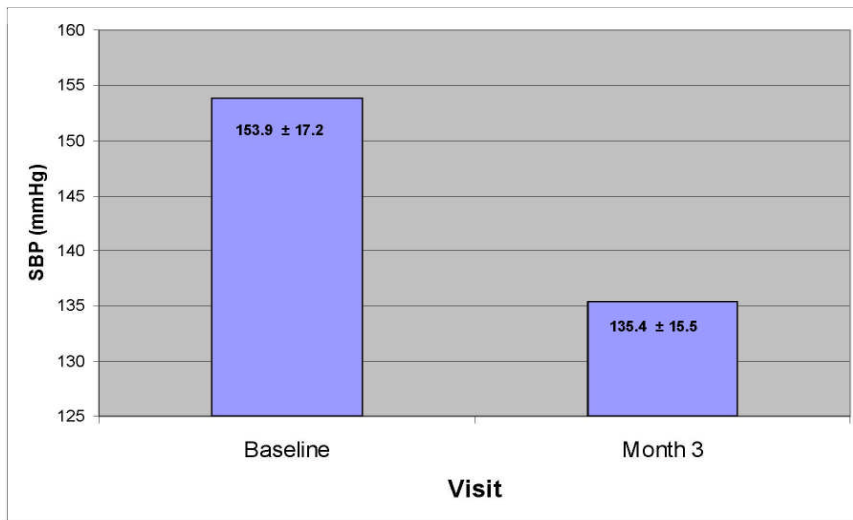
Efficacy Analysis

The following results consist of sitting blood pressure values taken by the treating physician during regular office visits. In the evaluable population (n=15,200), significant reductions in mean systolic (-18.5±19.3 mmHg, [95% CI-

18.78,-18.17], p<0.0001) and diastolic (-9.4±11.2 mmHg; [95% CI -9.55,-9.20], p<0.0001) blood pressure were observed after 3 months of therapy with valsartan / valsartan-hydrochlorothiazide (Figures 2 and 3).

FIG. 2 Primary Endpoint – Mean Systolic Blood Pressure by Visit for all Evaluable Patients (n=15,200)

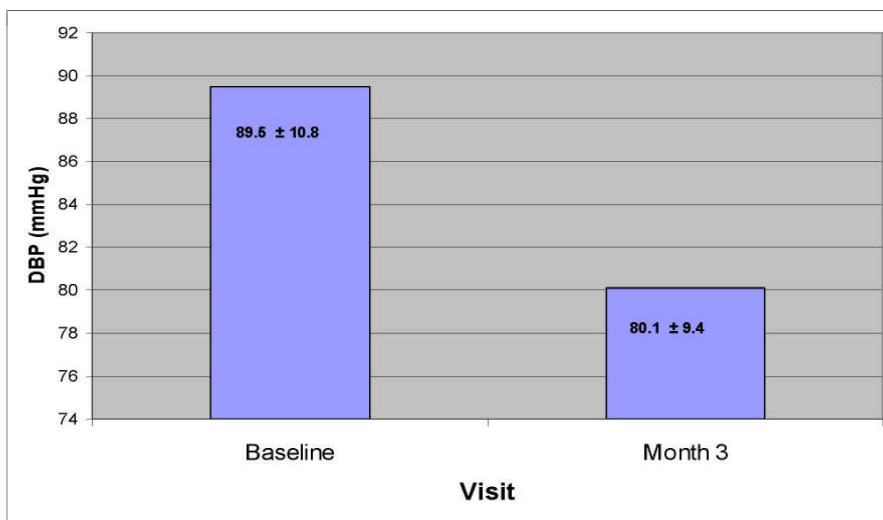
Figure 2.



2

FIG. 3 Primary Endpoint – Mean Diastolic Blood Pressure by Visit for all Evaluable Patients (n= 15,200)

Figure 3.



3

Patients with higher baseline blood pressure values experienced the greatest absolute reduction. For instance, patients with a mean systolic blood pressure of at least 180 mmHg (n=1,366) experienced a mean reduction of 43.6

mmHg, and patients with a mean diastolic blood pressure of at least 100 mmHg (n=3,234) experienced a mean reduction of 18.7 mmHg (Figures 4 and 5).

FIG. 4 Mean Change from Baseline in Systolic Blood Pressure by Value at Baseline for all Evaluable Patients (n=15,200)

Figure 4.

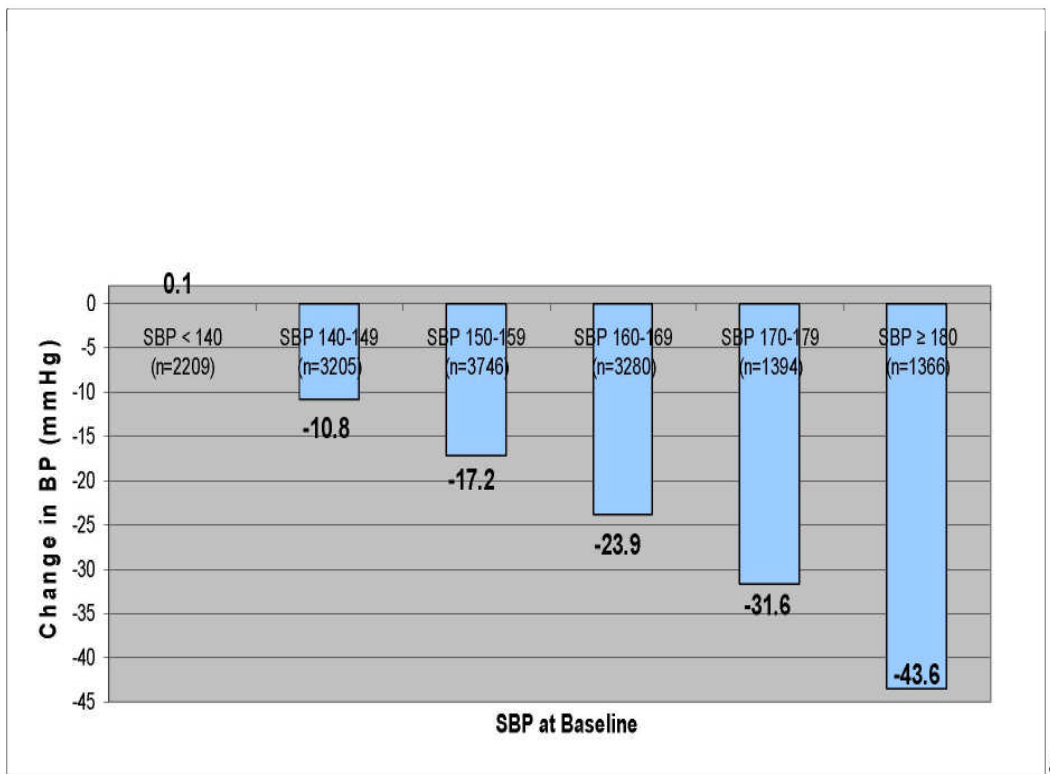


FIG. 5 Mean Change from Baseline in Diastolic Blood Pressure by Value at Baseline for all Evaluable Patients (n= 15,200)

Figure 5.

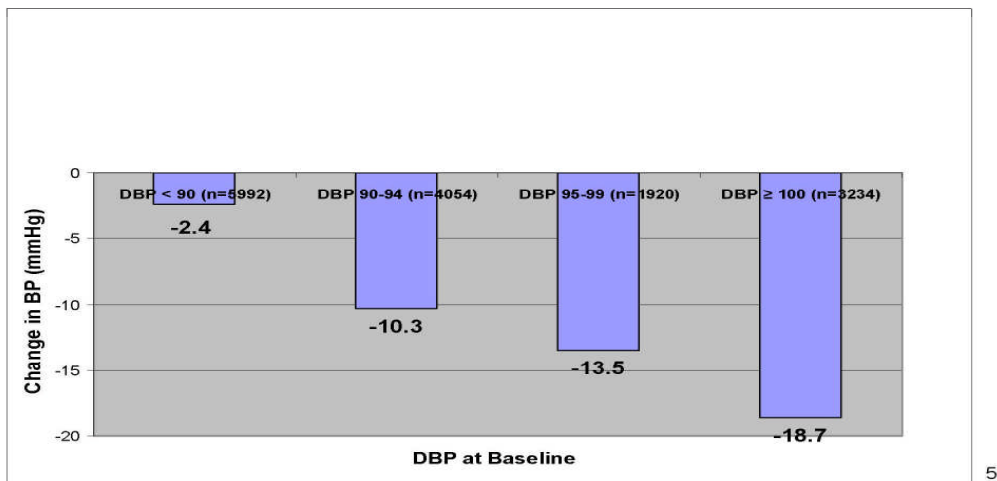
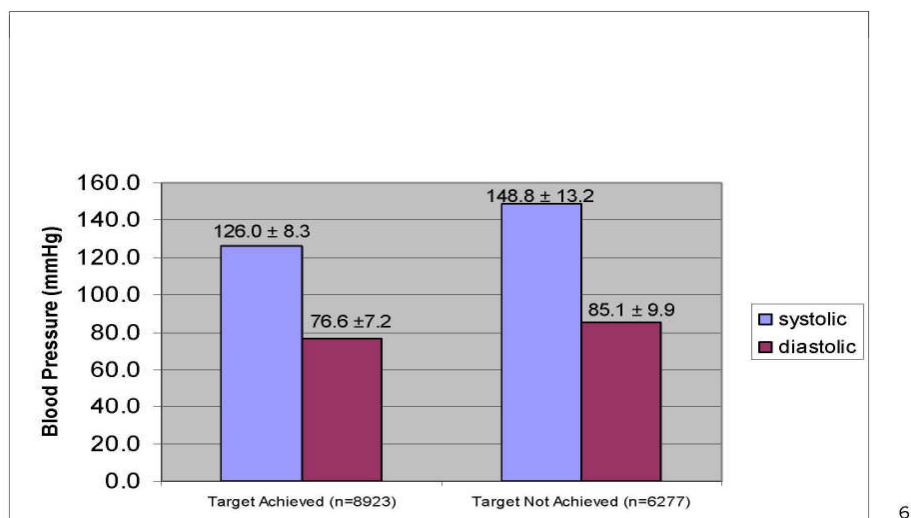


FIG. 6 Mean (\pm SD) Blood Pressure at month 3 by Target Blood Pressure (<140/90) Achieved or not for all Evaluable Patients (n=15,200)

Figure 6.



Fifty-nine percent of patients achieved target blood pressure (<140/90 mmHg) while the responder rates for systolic (10 mmHg or greater decrease or SBP<140 mmHg) and diastolic (10 mmHg or greater decrease or DBP<90 mmHg) blood pressures were 82% and 87%, respectively. For those patients in whom the target blood pressure was achieved (n=8,923, 59%), 88.5% received a physician recommendation at 3 months of no change in anti-hypertensive therapy. For those patients in whom the target blood pressure was not achieved (n=6,277, 41%), 55.1% received a physician recommendation of no change in therapy. The mean blood pressure for patients having achieved the recommended blood pressure target was 126.0/76.6 mmHg and 148.8/85.1

mmHg for those who failed to reach the target (Figure 6).

Eighty-six percent of evaluable patients reported taking their medication every day, while 8.1% and 0.8 % reported taking it almost every day or every other day, respectively. Patients who reported being compliant to prescribed study medication (n=14,189) experienced significantly greater systolic blood pressure lowering (-18.9±19.1 mmHg) and diastolic blood pressure (-9.6±11.1 mmHg) lowering as compared with non-compliant (n=764) patients (-10.3±21.3 and -5.5±12.1 mmHg, respectively) (p<0.0001). Subgroup analyses by age and gender were consistent with findings in the total study population (Table 2).

TABLE 2 Percentage of Patients Achieving Target Blood Pressure <140/90 mmHg after 3 Months in Study Cohorts

Study Cohort	% Patients Achieving Target	Mean Reduction (mmHg) SBP	Mean Reduction (mmHg) DBP
Evaluable patients (n=15,200)	59%	-18.5±19.3	-9.4±11.2
Compliance			
Compliant (n=14,189)	60%	-18.9±19.1	-9.6±11.1
Non-compliant (n=764)	34%	-10.3±21.3	-5.5±12.1
Race			
Caucasian (n=12,438)	59%	-18.9±19.2	-9.6±11.2
Black (n=455)	51%	-17.3±20.1	-8.2±11.2
Asian (n=1,509)	62%	-15.8±19.2	-7.8±10.4
Other (n=621)	60%	-18.1±19.2	-9.2±11.3
Gender			
Males (n=6,584)	58.9%	-17.7±18.5	-9.5±11.1
Females (n=6,750)	59.1%	-19.2±19.9	-9.2±11.2
Comorbidity			
Diabetics (n=2,977)	60%*	-16.0±19.3	-7.7±11.1
All other patients (n=12,223)	58%	-19.1±19.3	-9.8±11.2
Age			
≥65 years (n=5,369)	56%	-19.1±20.4	-8.2±11.2
<65 years (n=9,597)	60%	-18.1±18.6	-10.0±11.1

Diabetics (n=2,977) experienced a mean reduction in systolic blood pressure of 16.0 ± 19.3 mm Hg and a mean reduction in diastolic blood pressure of 7.7 ± 11.1 mmHg, and 22% of patients with diabetes reached their recommended treatment target of $<130/80$. The mean blood pressure for diabetic patients after 3 months of treatment was $135.2/78.1$ mmHg. Fewer diabetic patients were newly diagnosed hypertensive patients at baseline (23%) than in the overall population, and most were switched from a previous anti-hypertensive agent (51%).

DISCUSSION

The burden of cardiovascular disease in Canada is significant in financial terms as well as its impact on quality of life. The total cost of cardiovascular diseases on the health sector of the Canadian economy is estimated to be over \$18 billion, representing over 11% of the total cost of all illnesses, including indirect costs of approximately \$12 billion.^{18,19}

While cardiovascular disease is not restricted to the elderly, the prevalence increases with age. The percentage of all deaths due to cardiovascular diseases steadily increases after the age of 50 years among women and after the age of 40 years among men.¹⁸ Because of the growing elderly population in Canada, the burden of this disease is likely to increase in the future. As a result, the healthcare community faces significant challenges. Programs designed to control modifiable risk factors of cardiovascular disease are of primary importance. Hypertension (defined as a systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg) is a major risk factor for stroke, coronary artery disease, peripheral vascular disease, and congestive heart failure, and increases overall cardiovascular risk by 2 to 3 fold. Research evidence strongly supports the benefits of treating high blood pressure to reduce the incidence of stroke, myocardial infarction, ischemic heart disease, vascular disease, renal diseases, heart failure, and overall death rate.³⁻⁵

The early identification of patients with hypertension, initiation of effective lifestyle modifications and therapeutics, and strategies designed to optimize patient compliance are expected to have a significant impact on future

cardiovascular events and resulting disability and mortality. This large observational trial of valsartan with or without hydrochlorothiazide was designed to observe blood pressure reduction, compliance and regimen changes 3 months after initiation of therapy and optimized patient support.

Large observational studies have distinct limitations, but also have advantages, all of which must be considered in the interpretation of the results. In contrast to a randomized controlled trial, the present study does not have a control group. On the other hand, observational studies – and the current trial in particular – put the patient and physician in a less artificial situation, with broader inclusion and exclusion criteria that result in a patient population that is reflective of every day medical practice. Therefore, as one might expect, since the follow-up visit at month-3 was proposed as part of a regular medical practice visit rather than a protocol-driven requirement, month-3 data was provided for approximately 45% of all enrolled patients. Results of this interim analysis demonstrated that treatment was highly effective in reducing both systolic and diastolic blood pressure. A majority of patients achieved target blood pressure values per the Canadian Hypertension Education Program¹⁰ regardless of the specific valsartan regimen prescribed, gender, or age.

The greatest magnitudes of blood pressure reduction were in those patients with highest blood pressure values at baseline. This may be related in part to the regression to the mean phenomenon which has been observed and reported with other anti-hypertensive agents.²⁰ Interestingly, changes in anti-hypertensive regimen at the 3-month visit were not always ordered by the physicians, even in those patients who did not reach their target blood pressure goals. This finding may reflect physician's insight into patient lifestyle habits or treatment compliance not captured in this trial or it may indicate reluctance for aggressive treatment, favoring tolerability versus blood pressure control. Alternatively, it may reflect declines in blood pressure that were encouraging and significant enough to maintain the patient on the current valsartan-based regimen. Previous evaluations have demonstrated that physicians consider baseline blood pressure levels when determining

individual targets and that improvements in blood pressure from baseline may be considered sufficient by some of them, even if the target blood pressure, as dictated by guidelines, is not met.²¹ This study also demonstrated a high compliance rate at 3 months in a setting supportive of optimal compliance to a medication regimen. Further assessments are needed following longer term therapy since hypertension is a chronic condition and its management is a lifelong endeavor. Although all patients received a home blood pressure monitor, only 938 patients (2.8%) took advantage of the nursing support that was offered as part of this study. The relative impact of the various support tools on blood pressure reduction and overall compliance was not assessed in this study.

Hypertension is a common comorbid condition of diabetes and substantially increases the risk of both macrovascular and microvascular complications in a population already at high risk for cardiovascular disease.²² More aggressive treatment goals have been established for diabetic patients²³ and clinical trials have demonstrated that aggressive treatment of hypertension effectively reduces cardiovascular complications in this special population.^{15,24} In the Diovanage 4 trial, 22% of the diabetic patients reached the more aggressive treatment goal of <130/80 mmHg established for this population. While the percentage of controlled diabetics in this trial is more than twice that previously reported in Canada (9%)⁸ - improvement is needed and the reason for this treatment target gap should be further explored.

The overall interim results from the Diovanage 4 trial demonstrated the benefit of valsartan alone and valsartan with hydrochlorothiazide in the management of essential hypertension. Patients experienced a mean systolic blood pressure reduction of 18.5 mmHg and diastolic blood pressure reduction of 9.4 mmHg. These results are consistent with another recently completed observational trial, which demonstrated significant blood pressure control with valsartan and hydrochlorothiazide²⁵ along with good safety and tolerability. The relationship between blood pressure and cardiovascular risk is continuous and even small reductions substantially reduce cardiovascular risk. Due to the significant burden that

cardiovascular disease imposes on the Canadian society, continued efforts to control hypertension are of highest priority. Optimal management of hypertension along with heightened patient support for improved compliance are among health care strategies which may slow the burgeoning health care crisis facing Canada and the international community.

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